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COVID-19: Lessons from SARS and MERS

Introduction

In December 2019, a new pneumonic disease began to appear in Wuhan, Hubei Province, China. It seemed highly infectious and resistant to therapy, causing considerable concern amongst physicians. Within a month, 41 patients had been admitted to a single hospital and one had died. The initial cases were strongly associated with the Huanan seafood market, in which exotic animals were sold for food. The market was closed, but it was several weeks before public health officials were able to introduce strong public health quarantine measures in the local area.

Transmission and epidemiology

Within weeks of the first cases, a series of papers were released detailing the epidemiology of the disease (now termed COVID-19) [1-3]. By early January 2020 the virus was identified and the sequence determined. The virus (termed SARS-CoV-2) shares 88% sequence identity to two coronaviruses found in bats, bat-SLCoVZC45 and bat-SL-CoVZXC21, 79% identity with the Severe Acute Respiratory Syndrome (SARS) coronavirus and 50% identity with Middle Eastern Respiratory Syndrome (MERS) coronavirus [4]. From the first cohort of patients, 8 complete genomes were 99.9% identical in sequence. Given that the typical RNA coronavirus evolves at a rate of 10^4 nucleotide substitutions per year, this suggests a recent single source emergence in early December or late November 2019 [4]. SARS-CoV-2 is thought to be transmitted via contaminated hands, surfaces and aerosolised droplets; extensive human-to-human transmission is evident, with clusters of infected families and medical staff [5]. The number of confirmed cases has increased rapidly, at a rate that far outstripped the rate of rise of cases of SARS in 2002/3, raising serious global health concerns. By the 21st January, COVID-19 cases were widespread across mainland China, soon spreading beyond the Chinese borders.

On the 30th January 2020 the International Health Regulations Emergency Committee of the World Health Organization (WHO) declared a public health emergency of international concern. As of the 24th February 2020, there were 79,331 lab confirmed cases and 2,618 deaths worldwide [6]. The majority of these are in China with 77,262 cases and 2,595 deaths [6]. Clearly, many are still suffering from COVID-19 and may or may not recover. This is only a small fraction of the total population of China (1,428 million), and strenuous efforts continue to limit spread. However, SARS-CoV-2 has now spread to 29 countries, the Republic of Korea having the 2nd highest number of cases (893 cases with 8 deaths) [6]. In the UK there have been 13 confirmed cases, 8 of whom have recovered and been discharged home. As of 25th of February 2020, 276 cases and 7 deaths have been identified in 7 EU/EEA countries. The majority of these cases have been from a spike in locally acquired cases in Italy resulting in 6 deaths. Iran has also had a recent increase in cases with 61 cases and 12 deaths [7,8].

From the first 41 reported cases, the mortality rate was thought to be as high as 15%. The general fatality rate is currently uncertain but could be as high as 1–2% of all infections; however, as more cases are found with mild or unapparent disease this rate is expected to fall. The average incubation period is around 5 days, but also appears quite variable and may be as long as two weeks [3]. With around 60,000 active cases awaiting a final outcome, the case fatality amongst those with COVID-19 is difficult to determine at the present time. One case in Egypt is the first detected in Africa, while many developing, low resource, countries have had no cases. This apparently low transmission rate to such countries might be a consequence of public health measures enforced to limit spread of SARS-CoV-2 in China, or could reflect the limited diagnostic capacity in low resource settings.

SARS-CoV-2 seems to have a predilection for the elderly male population and for patients with co-morbidities. The most common symptoms include fever (83%), cough (82%) and breathlessness (31%) [1, 2]. The majority (75%) of patients had bilateral pneumonic changes on CT imaging [2]. In a recent update by the Chinese Centre for Disease Control, 81% of infections were considered mild and only 1.2% asymptomatic [9]. The first report to detail infection in children found only 9 cases of COVID-19 in children; 7 were female and none required intensive care support, potentially indicating that children may be less susceptible to infection and/or symptomatic disease [10].

Comparisons with other lower respiratory tract infections

Lower respiratory tract infections are the most deadly communicable diseases globally, causing 3 million deaths per year and are the 4th commonest cause of death worldwide, including endemic, epidemic and pandemic viruses. In 2009 the influenza (H1N1) pandemic spread to 214 countries and caused an estimated 500,000 deaths with a case fatality rate of around 0.2% [11].

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Table 1. Comparison of number of cases and deaths after time of first detection, relative to MERS, SARS

	Location of Origin	Year	Cases	Deaths	Case Fatality	R0*	Countries with confirmed cases	Reference
SARS	Guangdong, China	2002-2003	8,422	916	11%	2-4	29	[12]
MERS	Saudi Arabia	2012	2,494	858	34.4%	1	27	[13]
COVID-19	Wuhan, China	2019-present#	79,331	2,618	~1–2%	2.2	29	
pH1N1 Influenza	North America	2009		500,000**	0.2%**		214	[11]

* R0: Basic Reproduction Number (the number of cases resultant from each index case)
# Accurate as of 24th February 2020
** estimated

There are numerous other coronaviruses that are pathogenic to humans but present with mild clinical symptoms. However, SARS-CoV-2 is the 3rd highly pathogenic coronavirus to emerge in the past 2 decades. The first outbreak was SARS, in 2002 in the Guangdong province of China in 'wet markets' (like the Huanan market where SARS-Cov-2 is thought to have first emerged). In total, there were 8,422 cases of SARS with 916 deaths across 29 countries. The estimated case fatality for SARS was 11% [12]. Middle Eastern Respiratory Syndrome (MERS) coronavirus was responsible for the severe respiratory disease outbreak in 2012 in the Middle East. There were 2,494 confirmed cases with 858 fatalities; 38 deaths were reported in South Korea, with a total of 27 countries reporting cases of MERS (Table 1) [13].

Like SARS-CoV-2, SARS and MERS coronaviruses are thought to have originated from bats and transmitted to humans from an intermediate host, civets and dromedary camels respectively. For SARS-CoV-2, the zoonotic source and intermediate host is yet to be confirmed but with recent advances in whole genome sequencing, detailed phylogenetic analysis can be rapidly performed and used to establish detailed evolutionary links.

The improved ability to identify and diagnose novel pathogens has enabled a rapid global response to minimise the impact and co-coordinate international resources; however, the effect that this will have on the global impact of COVID-19 remains unknown. One of the first measures taken by the local authorities was alerting the WHO within 4 weeks from the first patient being identified. This is in stark contrast to the SARS outbreak when it took 4 months. The identification of a novel coronavirus in the SARS-CoV-2 outbreak was quickly followed by the closure of the Huanan market, with the aim of preventing any further zoonotic transmission. During the SARS outbreak there was a delay in identifying the civet as a reservoir for the disease and civets continued to be sold on food markets. Steps such as closing the market has encouraged identification and reduction of transmission from potential animal sources and the WHO has advised that caution should be taken to avoid unprotected contact with farm or wild animals [6].

Outlook and case management

For now, the reported case numbers of COVID-19 continues to mount, but more slowly. However, with such widespread distribution both within and outside China, it seems likely that subsequent outbreaks will continue to be seen. Crucially there are substantial gaps in our knowledge regarding the epidemiology of disease, the major predisposing risks, transmission rates, clinical manifestations and phenotypes and treatment options. However, we have learnt much from the SARS and MERS outbreaks, which influenced the local and global response to the current outbreak. Our ability to rapidly identify novel pathogens using whole genome sequencing and to develop PCR based diagnostic tests from this data has expedited our ability to identify cases and understand the epidemiology of disease much earlier in the epidemic. This has informed the current strategy of reducing human to human transmissions, especially to healthcare professionals.

Another key strategy to reduce transmission is to correctly triage and identify patients with severe acute respiratory infections at first point of contact to minimise exposure to others. The epidemiological and clinical criteria must be met to be classified as a possible case. Currently anyone with severe respiratory infection requiring hospital admission with no alternative diagnosis and a travel history to an affected country during the 14 days before the onset of symptoms, or anyone with any acute respiratory illness and contact with a confirmed or probable case of COVID-19 (including in a health care facility) falls under a suspected case definition [14]. These case definitions vary slightly in different countries and Public Health England (PHE) include clinical or radiological evidence of pneumonia, specific symptoms of breathlessness or cough, or anyone with a fever who has a history of travel to the listed countries [15].

For the public, general precautions should be taken to avoid contact with patients suffering from acute respiratory infections. In health care settings, precautions such as using good hand hygiene, and the use of personal protection equipment (PPE) to avoid direct contact with patient's secretions or bodily fluids should be followed. Specimens should be tested for routine bacterial and viral infections, as well as using both upper and lower respiratory tract samples to test for SARS-CoV-2. This should be performed using real time polymerase chain reaction testing (RT-PCR). Serological tests are in development but should only be used if RT-PCR is not available [16]. A key part of infection control is detailed contact tracing.

Early supportive measures should be taken, including supportive oxygen therapy for respiratory distress and hypoxia, more invasive respiratory support if required, intravenous fluids, antimicrobials and anti-viral medications. The current published data indicates a long mild incubation period followed by rapid progression of disease with 8 days being the median time from initial symptoms to the

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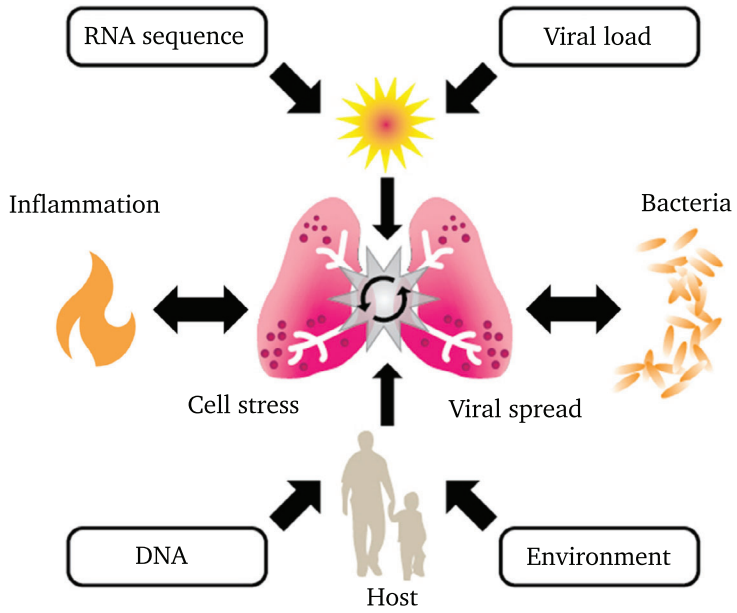

Figure 1. Possible determinants of COVID-19 severity. Many factors can contribute to the severity of lower respiratory tract infections. The sequence of the viral genome and the degree of viral replication (viral load) can influence severity and initiate an inflammatory response that can cause immunopathology. The airway microbiome and bacterial co-infections can similar increase severity. Some hosts are more susceptible to severe disease based on genetic and environmental factors.

onset of breathlessness, 9 days to acute respiratory distress syndrome (ARDS) and 10.5 days to admission to intensive care [1]. In one study of 99 cases, 17% developed ARDS, 13% required non-invasive respiratory support, 4% needed invasive ventilation and 3% needed extracorporeal membrane oxygenation (ECMO) [2]. Tools such as the MuLBSTA Score, which incorporates risk factors and comorbidities such as smoking, hypertension, age, bacterial co-infections, lymphopenia and areas of the lung involved, may be useful to predict mortality in patients with viral pneumonia [2, 17].

Therapeutic prospects

The SARS and MERS epidemics, and our treatment of other endemic and epidemic respiratory viruses, can provide some guidance on treatment strategies that may benefit patients with COVID-19. There are currently no specific anti-COVID-19 therapies but over 80 clinical treatment trials have been initiated to tackle COVID-19 [18]. These trials include the HIV drug combination of lopinavir and ritonavir (protease inhibitors that have been reported to reduce SARS and MERS replication), and also remdesivir (an approved reverse transcriptase inhibitor that similarly has demonstrated *in vitro* activity against SARS-CoV-2 [19]). It may also be possible to enhance the protective host immune response to infection, or inhibit immunopathogenesis (which is thought to contribute to disease severity for some respiratory pathogens). In particular, 'cytokine storms' are thought to be major contributors to the severity of many lower respiratory tract infections, such as influenza [20] and SARS [21]. Host-targeted therapies might therefore be aimed at either enhancement of innate immune clearance of SARS-CoV-2 or inhibition of inflammatory damage to the airway and the development of secondary bacterial pneumonias. In the first 41 cases, 22% were given systemic corticosteroids, with the aim of suppressing inflammation induced lung injury [1]; however, current WHO guidelines do not recommend their use and data from SARS and MERS showed that corticosteroids did not reduce mortality and potentially delayed viral clearance [22-24]. Alternative strategies under investigation include immunomodulation with chloroquine (which might also have anti-viral function [19]), monoclonal antibodies and immunoglobulins. These interventional studies, in addition to observational studies, will develop our understanding of severe COVID-19 infections, particularly the relative contribution of viral load and sequence (though current data indicate little strain variation amongst cases so far), bacterial co-infections, host genetics, environmental factors and immunopathogenesis (Figure 1).

Summary

The SARS and MERS epidemics have put us in a better position to respond to COVID-19. The transparency demonstrated in the rapid sharing of the SARS-CoV-2 genetic information has been critical in mediating a global approach to minimise the spread of disease. This has enabled the rapid development of diagnostic tests and their global implementation. In turn these diagnostic tests have facilitated the management of cases in those areas most affected, and the identification of cases in other countries, all of which has aided in limiting the global spread of SARS-CoV-2. However, current evidence indicates that these public health measures alone may be insufficient to eliminate COVID-19. New treatments are urgently needed and the time that public health measures have bought us must be used productively. Ongoing clinical trials of existing drugs may provide further breakthroughs in limiting morbidity and mortality, but vaccines and prophylactics may be needed to prevent the spread of infections.

Conclusions

In a little over two months SARS-CoV-2 has spread to 29 countries and caused far greater morbidity and mortality than either SARS or MERS, despite rapid identification and robust public health measures. The outlook is uncertain, but continued global spread seems likely and we must be prepared to face this threat. While continuing to delay the spread of disease we must rapidly initiate studies of potential therapeutics and develop our understanding of COVID-19 pathogenesis.

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Note

All numbers in this article are correct as of 24 February 2020. As the situation regarding COVD-19 is changing daily, readers are recommended to refer to the websites listed in the references for the most up-to-date information.

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